Regarding: "Expression of myosin heavy chain isoforms in skeletal muscle of patients with peripheral arterial occlusive disease"

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The article by Steinacker and colleagues provides new insights into the pathophysiology of peripheral arterial disease (PAD). PAD is associated with major impairments in limb function. Patients with claudication have reduced exercise performance because of skeletal ischemia during exercise. This leads to marked limitations in daily walking activity, and thus, patients are unable to meet the physical function demands of daily activities. In contrast, patients with critical leg ischemia have reduced blood flow at rest, which therefore leads to symptoms of ischemic rest pain, ulceration, and gangrene. These individuals have restricted ambulation, poor muscle function, inability to heal distal lesions, and they are at risk of limb loss.

The pathophysiology of the clinical manifestations of PAD is initiated by the reduction in limb blood flow as the result of atherosclerotic occlusion of the major conduit vessels to the lower extremity. In patients with claudication, the metabolic demand of lower extremity skeletal muscle is relatively low at rest. Patients with claudication have adequate perfusion to skeletal muscle, skin, and other tissues in the leg to maintain healthy resting metabolic rates. However, with exercise, there is a marked increase in skeletal muscle metabolism that in healthy individuals results in a 20-fold to 40-fold increase in skeletal muscle blood flow and oxygen delivery.[1] In contrast, patients with claudication have blood flow that is unable to appropriately increase during exercise, which results in a supply-demand mismatch that leads to skeletal muscle ischemia.[1] Although the initial insult in the patient with claudication is clearly hemodynamic, the severity of the symptom cannot be totally explained by reduced blood flow alone. For example, measurements of calf blood flow or ankle blood pressure do not correlate well with treadmill exercise performance.[2,3] Thus, other factors that affect skeletal muscle metabolism and function must also play a significant role in determining the clinical severity of claudication.

During daily ambulatory activity, patients with claudication have several episodes of skeletal muscle ischemia followed by reperfusion when they stop and rest to relieve the claudication pain. This then leads to an increase in oxidant stress and the potential for free radical injury to skeletal muscle.[4] Several studies have evaluated these concepts with the assessment of changes in skeletal muscle in PAD with the muscle biopsy technique. In particular, patients with unilateral disease were selected for study to allow comparisons between the affected and unaffected legs. The results of these studies have shown that, in patients with claudication, there is marked evidence of skeletal muscle denervation of the distal motor nerves of the gastrocnemius muscle.[5,6] The denervation is confined to the affected limb and is associated with skeletal muscle atrophy and weakness.

In addition to muscle denervation, a number of metabolic abnormalities have also been described in the affected muscles of patients with claudication. Muscle mitochondria are the cellular site of oxidative energy production for muscle contraction. PAD is associated with mitochondrial DNA injury and altered expression of mitochondrial enzyme activities.[7] Further evidence of impaired metabolism

From the Health Sciences Center, University of Colorado.
Competition of interest: nil.
J Vasc Surg 2000;31:611-2.
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0741-5214/2000/$12.00 + 0 24/9/102849
doi:10.1067/mva.2000.102849

comes from the observations of changes in skeletal muscle carnitine metabolism. Carnitine is an important cofactor that provides a buffer molecule for the acyl-CoA pool. During healthy metabolic conditions, there is a rapid flux and turnover as fatty acids, proteins, and carbohydrates are converted to acyl-CoA intermediates to be used in the Krebs cycle for further oxidative metabolism. During skeletal muscle ischemia, this process is interrupted, which leads to the accumulation of acyl-CoA intermediates.[8] This then leads to the formation of acylcarnitines. For example, the accumulation of acylcarnitines has been observed in ischemic skeletal muscle in patients with claudication.[8] Further, patients with the greatest accumulation had the lowest treadmill exercise performance. Thus, alterations in skeletal muscle neurologic and metabolic function provide insight into the pathophysiology of the disease. The reduced skeletal muscle blood flow is an initial event, but ischemic injury leads to a more complicated and disabling clinical scenario.

The study by Steinacker and colleagues extends these findings with the evaluation of changes in skeletal muscle myosin isoforms in the different clinical stages of PAD. Skeletal muscle isoforms in part determine the different muscle fiber types that can be divided into two major categories. Type I oxidative, slow twitch fibers have large numbers of mitochondria and are used to sustain repetitive muscle contractions under aerobic conditions over long periods of time. In contrast, type II glycolytic, fast twitch fibers have fewer mitochondria but generate more force during contraction. These fibers are used to produce rapid muscle contractions but have easy fatigability. Thus, changes in skeletal muscle isoforms may be important in terms of understanding how skeletal muscle adapts to chronic ischemia.

Steinacker and colleagues observed that the type I myosin isoform was increased in both Fontaine stage 3 and 4 and was associated with a corresponding decrease in type IIb isoforms in the same patients. In contrast, type IIa isoforms were reduced only in Fontaine stage 4. These results are consistent with previous histologic study results that show a decrease in type 2 skeletal muscle fibers in patients with claudication.[5]

Although these studies are provocative, there are several limitations to the observations. Patients were mainly enrolled with different clinical grades of severity. What is lacking is any functional correlation to the differences in muscle isoforms. This would be particularly important to determine whether the changes in muscle isoforms are associated with reduced muscle strength and muscle performance. Also limiting is the inability to distinguish whether the changes in muscle isoforms result from reduced blood flow per se or other factors, such as age, inactivity, and oxidant stress.

In summary, PAD in fact has a complex pathophysiology. The clinical manifestations are initiated in claudicants by decreased oxygen delivery during exercise and in critical leg ischemia by reduced flow at rest. However, the disease pathophysiology is not simply explained by reductions in flow. Alterations in the skeletal muscle end organ are critically important in defining the functional limitations of the patient. Future studies need to further explore these changes in skeletal muscle to define whether they may serve as new targets for therapeutic interventions.

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Submitted Aug 6, 1999; accepted Aug 26, 1999.

Please see the related article by Dr Jürgen M. Steinacker et al on pages 443-9.